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研究課題名（和文）Learning to control brain activity pattern using real-time functional MRI: A feasibility study

研究課題名（英文）Learning to control brain activity pattern using real-time functional MRI: A feasibility study

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研究成果の概要（和文）：本研究では、即時に脳機能状態を識別して可視化する、リアルタイム機能的MRIによる脳機能識別システムを独自に開発し、被験者が自分の脳の状態を観察しながら、目的とするパターンに制御する、つまり、ニューロフィードバック制御、の可能性について検証した。結果では、開発したシステムは、全体の処理を、画像取得時間（2秒）よりも速く行う事が出来た。3つのタスク（指を鳴らす行為を想像、語想起、引き算）について、リアルタイム機能的MRIを撮像しながら、被検者に識別、再現させるフィードバック実験では、サポートベクターマシンを用いる事により、一貫して80%以上の平均識別精度で、目的とする脳状態を再現する事ができた。

研究成果の概要（英文）：In this study, a real-time fMRI-based brain state decoder system to identify different brain states, viewed as brain activity pattern, was developed and used to investigate whether participants can control their brain activity pattern to match a pre-determined target pattern using neurofeedback. The system attained an overall processing time that was faster than the image acquisition time set at 2s. Using support vector machines, brain states associated with three tasks (imagined tapping, word generation, and serial subtraction tasks) were successfully reproduced as evidenced by the consistently high mean classification accuracy of greater than 80% during feedback scans.

研究分野：生物物理工学

キーワード：real-time functional MRI　neurofeedback　support vector machine　brain machine interface　machine learning

１．研究開始当初の背景

Real-time functional magnetic resonance imaging (fMRI) is a non-invasive technique that enables the reconstruction and analysis of functional magnetic resonance images as the images are acquired. With real-time fMRI, it is possible to observe the activity of the brain while one thinks, feels, or learns. This gives rise to several new and innovative ways of studying brain function. Combined with machine learning approaches, such as support vector machines (SVM), real-time fMRI has enabled the real-time classification or decoding of different brain states. The decoded brain state, a reflection of the activity of the whole brain, could then be employed to provide a feedback signal for participants to regulate, or a signal to control a brain computer interface system.

２．研究の目的

The purpose of the study is twofold. First, it aims to develop a working prototype of a real-time fMRI-based brain state decoder system in Nagoya University's Brain and Mind Research Center. Second, it also aims to examine the feasibility of whether participants can control their brain activity pattern to match to a pre-determined target pattern using real-time neurofeedback training.

３．研究の方法

(1) Real-time brain state decoder system

The conceptual design of the system is outlined in Figure 1. It consists of 3 subsystems: 1) image acquisition subsystem, 2) real-time analysis subsystem, and 3) presentation subsystem. The image acquisition subsystem, consisting of the MRI scanner and its console, is responsible for MR image acquisition, real-time image reconstruction, and real-time image transfer to the analysis subsystem. On the other hand, the real-time analysis subsystem, consisting of a dedicated workstation running the Linux operating system, is responsible for the real-time analysis of the acquired MR images including 1) real-time image preprocessing such as realignment, normalization, smoothing, and masking, 2) statistical analysis using the general linear model to identify activation regions, and 3) real-time brain state decoding/classification using machine learning algorithms, among others. These methods are currently implemented in a supporting software package called *Guava*, which runs on Matlab. Depending on the experimental design, this subsystem also generates the needed signals for stimulus or feedback. The presentation subsystem is responsible for the presentation of stimuli as well as feedback signals to the participant inside the MRI scanner. Currently the subsystem supports screen-projector combination for simple stimuli and feedback presentations as well as video camera-small humanoid robot combination for brain machine interface (BMI) applications.

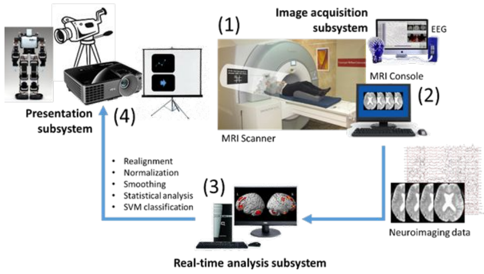

Figure 1. Schematic representation of the implemented real-time functional MRI system.

(2) Participants

For the imaging study, 33 participants were recruited from Nagoya University. The study was approved by the ethical committee of Nagoya University School of Medicine with approval number 2014-0272. All participants gave written informed consent before participating in the study.

(3) Experimental paradigm and tasks

All participants underwent functional MRI scanning at Nagoya University's Brain and Mind Research Center. Each scanning session consisted of the following scans: 1) an anatomical localizer run, 2) 3D MPRAGE scan for a reference anatomical image, and 3) 4 task-based functional MRI scans. The 4 task scans were designed in a block manner and included a pre-training scan and 3 feedback scans.

The pre-training scan consisted of rest and task blocks alternated with each other with each block lasting for 30s. The tasks included an imaginary finger tapping task (MOTION task), a word-generation task (WORD task), and a serial subtraction task (COUNT task). For the MOTION task, the participants were instructed to imagine tapping their thumb and index finger in both hands at their own pace. For the WORD task, participants were instructed to generate as many words related to "things inside the house" as possible. For the COUNT task, participants were instructed to initially think of a three-digit number, then sequentially subtract the number 7 from it. If the difference reached 0 or negative number, they had to think of another 3-digit number again and had to repeat the same process. After the pre-training scan, a support vector machine was trained online using the obtained functional images to classify the different brain states associated with each task. The trained SVM classifiers were then used in the succeeding feedback scans.

The three feedback scans consisted of two blocks for each task giving a total of 6 task blocks. During the task blocks, participants were asked to control the movement of an arrow (representing the feedback signal) by matching their ongoing brain state (brain activity pattern) with that associated with the target task displayed on screen. If the participant's ongoing brain state matched with the target state as identified by the trained SVM, the arrow would move to the right. The better the participant matched the target brain state, the farther the arrow would move.

Questionnaires were also administered including MoCA (Montreal Cognitive Assessment), SDST (symbol digit substitution test), word generation (before and after the scan) where participants had to write on a piece of paper as many words related to things inside the house as possible within 1 min, and a post-scan questionnaire to evaluate the participants' performance during feedback scans.

(4) Imaging

Functional and anatomical scans were acquired using a Siemen's Magnetom Verio (Siemens, Erlanger, Germany) 3.0T scanner with a 32-channel head coil. T1-weighted MR images were acquired using a 3D MPRAGE (Magnetization Prepared Rapid Acquisition Gradient Echo, Siemens) pulse sequence from all participants for anatomical reference with the following imaging parameters: TR = 2.5s, TE = 2.48ms, 192 sagittal slices with a distance factor of 50% and 1mm thickness, FOV = 256mm, 256 x 256 matrix dimension, and in-plane voxel resolution of 1.0 x 1.0 mm^2. For the task fMRI scans, the following parameters were used: 31 axial slices with a 25% distance factor, FOV = 192 mm, slice thickness = 4.0 mm, TR = 2.0s, TE = 30ms, flip angle = 80 degrees, 64 x 64 matrix dimension, voxel size = 3 x 3 x 4 mm^3, 375 volumes for the pre-training scan and 195 volumes for the feedback scans.

(5) Image preprocessing

All imaging data were preprocessed using SPM12 (Wellcome Trust Center for Neuroimaging, London, UK). T1-weighted images were first segmented into component images including gray matter, white matter, cerebrospinal fluid, and non-brain tissues. For each functional data, the first 5 volumes were discarded to account for the initial image inhomogeneity. The data were then realigned, co-registered to the anatomical image, normalized to standard space, resampled to an isotropic voxel resolution equal to 2 x 2 x 2 mm^3, and smoothed using an 8-mm FWHM Gaussian filter.

(6) Offline analysis of task fMRI datasets

Offline analyses were also performed for the task fMRI datasets (pre-training and feedback scans) using SPM12 to identify regions activated during each task. We used a box-car convolved with the canonical hemodynamic response function to model each task. To account for head motion, we also included the 6 estimated motion parameters in the model as nuisance regressors. Contrast images were extracted for each task and group results were obtained using a one-sample t-test with the contrast images as input. Significant voxels were identified using a threshold value of $p < 0.05$ corrected for multiple comparison using family-wise error cluster level correction (FWEc) with cluster defining threshold set to $p = 0.001$.

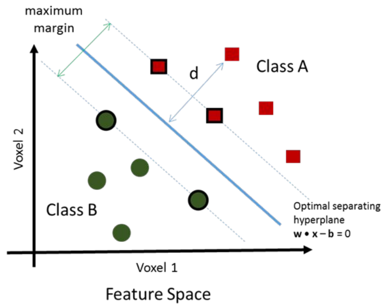

Figure 2. SVM model with a hypothetical 2-voxel feature space.

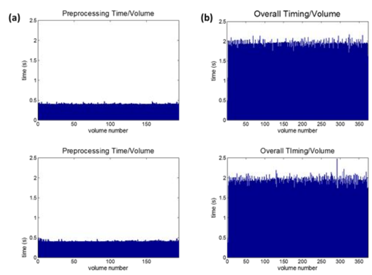

Figure 3. Representative timing data from two scanning sessions.

(7) Support Vector Machine

To identify the brain states associated with the different tasks used in the study, SVMs were used for both real-time and offline analyses. In general, given two classes of objects, SVM attempts to determine a separating hyperplane (decision boundary) optimizing the separation between the two groups (see Figure 2) using the provided training samples. The obtained model can then be used to classify new samples not yet seen by the SVM algorithm.

In this study, functional images from the pre-training scan were used as training samples to generate classification models for the different tasks. Here, we used several SVM classification models including Rest vs MOTION (to classify brain activity patterns during rest blocks and MOTION task blocks), Rest vs WORD, Rest vs COUNT, MOTION vs ALL (to classify brain activity patterns during MOTION task blocks and all other blocks including rest, WORD, and COUNT blocks), WORD vs ALL, and COUNT vs ALL. The trained SVMs were then used to classify, in real-time, the different brain activity patterns during the feedback scans. We computed the accuracy, task predictive value, and distance *d* (see Figure 2) to evaluate SVM's performance.

4. 研究成果

(1) System performance

Figure 3 shows representative timing performance of the implemented real-time fMRI system. Image preprocessing time per image volume (64 x 64 x 31 in size) was consistently less than 0.5s for the duration of the scan (Fig 3a). On the other hand, the overall timing per image volume including real-time image reconstruction, functional image transfer from the MRI scanner, image preprocessing, feedback presentation, as well as waiting time for the next image to arrive was less than scan repetition time set to 2.0s (Fig 3b). The system thus achieved a fully real-time processing capability.

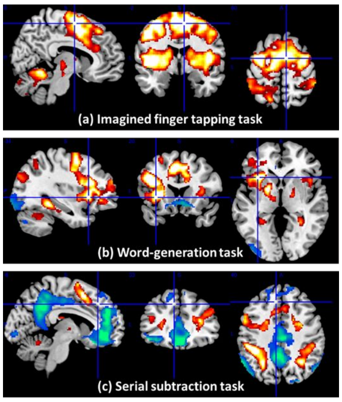

Figure 4. Pre-training group activation maps for the 3 tasks. Images are displayed using neurological convention (Left is left).

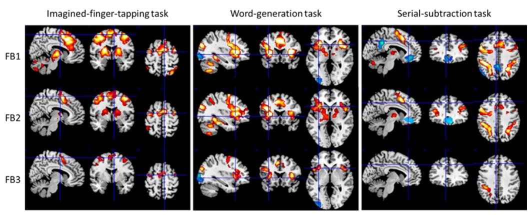

Figure 5. Group activation maps of the different tasks during feedback scans. FB1 – feedback scan 1, FB2 – feedback scan 2, and FB3 – feedback scan 3

(2) Task activation patterns

Figure 4 shows the group activation maps of the 3 tasks used in the study during pre-training scan. For the MOTION task, a large activated cluster with peak in the right postcentral gyrus/BA40 and another cluster in the right cerebellum were observed. Deactivation was observed in the left lingual gyrus. On the other hand, several activations were observed in the right cerebellum, left middle frontal gyrus, left medial frontal gyrus/BA6, right extra nuclear, and right parahippocampal gyrus for the WORD task. The right precuneus/BA31, right anterior cingulate gyrus/BA32, right supramarginal gyrus, and left inferior occipital gyrus/BA18 were deactivated. Finally, the COUNT task activated the visuospatial network nodes including the bilateral inferior parietal lobule, right and left cerebellum, and right extra nuclear and deactivated nodes in the default mode network including the posterior cingulate cortex (PCC)/precuneus, left medial frontal gyrus, bilateral inferior frontal gyrus, right superior temporal gyrus, and left cerebellum. The full list of activated regions and the MNI coordinates of the peak activations is given in Table 1.

Table 1. Group activation during pre-training scan. MNI coordinates of the peak location, cluster size, z-value, and regions.

TASK	X	Y	Z	cluster size	Z value	Regions
COUNT						
Activation	28	-62	-26	2900	6.02	R cerebellum, declive
	-24	-58	-32	975	5.58	Left cerebellum, anterior lobe
	28	28	4	11111	5.48	Right extra-nuclear
	-40	-40	44	2520	5.42	Left inferior parietal lobule
	50	-30	46	1822	5.32	Right inferior parietal lobule
Deactivation	-4	44	-10	5659	5.85	L medial frontal gyrus
	-32	18	-16	8912	5.76	Left inferior frontal gyrus
	48	-58	26	4168	5.59	Right superior temporal gyrus
	-24	-80	-32	321	5.28	Left cerebellum, uvula
	0	-56	50	4907	5.07	Left precuneus
	32	20	-20	3045	4.84	Right inferior frontal gyrus
MOTION						
Deactivation	-10	-88	-2	635	4.98	Left lingual gyrus
Activation	64	-30	20	46566	6.85	Right postcentral gyrus/BA40
	32	-56	-24	5462	5.60	Right cerebellum, declive
WORD						
Activation	32	-70	-48	7026	6.79	Right cerebellum
	-42	22	24	11785	6.06	Left middle frontal gyrus
	-4	14	52		6.01	Left medial frontal gyrus/BA6
	20	6	14	1012	4.95	Right extra nuclear
	36	-34	-12	559	4.42	Right parahippocampal gyrus
Deactivation	6	-52	32	278	4.45	Right precuneus/BA31
	14	24	-12	872	4.44	Right anterior cingulate/BA32
	58	-56	36	544	4.33	Right supramarginal gyrus
	-38	-86	-16	1501	4.31	Left inferior occipital gyrus/BA18

Table 2. Total number of active voxels (activated and de-activated) in the group activation maps for the 3 tasks used in the study. Pre – pre-training scan; FB1 – feedback scan 1; FB2 – feedback scan 2, and FB3 – feedback scan 3.

TASK	Pre	FB1	FB2	FB3	TOTAL
COUNT	46,340	24,211	19,252	769	90,572
MOTION	52,663	41,525	19,927	3,744	117,859
WORD	23,577	22,246	24,851	6,938	77,612
TOTAL	122,580	87,982	64,030	11,451	286,043

Figure 5 shows the group activation maps during feedback scans (top to bottom) for the different tasks (left to right). Based on this figure, similar regions were mostly activated during the feedback scans as compared to that during the pre-training scan, although a decreased in the number of activated voxels could be observed. This can be seen in Table 2, where a significantly large number of voxels were active during pre-training scan, followed by a decreasing trend for each succeeding feedback scans.

Table 3. SVM classification performance during feedback runs (offline). FB1 – feedback scan 1; FB2 – feedback scan 2; FB3 – feedback scan3; RvsM – rest vs MOTION; RvsW – rest vs WORD; RvsC – rest vs COUNT; MvsA – MOTION vs ALL; WvsA – WORD vs ALL; CvsA – COUNT vs ALL; ACC – accuracy; TPV – task predictive value

	Model	ACC (%)	TPV (%)	Model	ACC (%)	TPV (%)
FB1						
	RvsM	71.49	81.57	MvsA	61.76	84.51
	RvsW	77.96	88.43	WvsA	67.21	92.35
	RvsC	76.79	86.47	CvsA	64.02	87.45
FB2						
	RvsM	72.44	84.51	MvsA	62.32	83.14
	RvsW	74.48	87.45	WvsA	64.61	88.82
	RvsC	77.06	87.06	CvsA	65.20	87.45
FB3						
	RvsM	72.31	82.94	MvsA	63.10	87.25
	RvsW	72.53	84.31	WvsA	62.97	84.12
	RvsC	73.57	81.57	CvsA	62.48	82.16

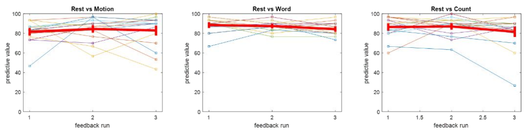

Figure 6. Individual (thin lines) and average (thick line) task predictive values for rest vs task (MOTION, WORD, COUNT) classification models during feedback runs.

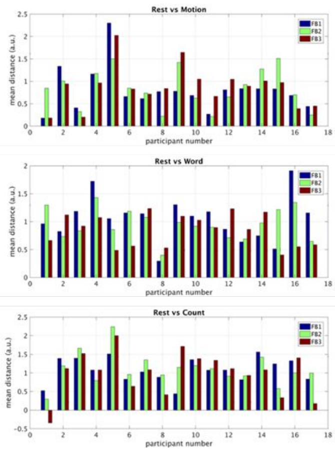

Figure 7. Individual average distance measure for each feedback scans. FB1 – feedback scan 1; FB2 – feedback scan 2; FB3 – feedback scan 3

(3) SVM classification performance

SVM classification performance is summarized in Table 3. Accuracies for rest vs task (MOTION, WORD, COUNT) models were above 70%, while task predictive values were all above 80%. The relatively low classification accuracies may be due to the possibility of participants practicing the tasks during rest blocks instead of just doing nothing. Classification accuracies for task (MOTION, WORD, COUNT) vs ALL models were only a little above 60%. But the task predictive values were again all above 80%. These low accuracies could also be due to the misclassification of images during rest blocks. The high predictive values for all tasks, however, indicate that the trained SVMs were able to successfully identify the associated brain activation patterns for these tasks.

Individual and average task predictive values are shown in Figure 6. Although individual differences in SVM performance can be observed, a paired sample t-test showed no significant change in the predictive values between feedback scans in all 3 tasks. This indicates that on average, the performance of the trained SVMs was consistent throughout feedback scans. Computed distance measures (Figure 7) also showed individual variability for each feedback scan, but overall, no significant change was observed.

(4) Correlation with behavioral measures

Several SVM performance measures showed correlation with SDST scores. Task predictive values for rest vs WORD classification model during feedback scan 1 positively correlated with pre- (r = 0.539) and post-scan (r = 0.541) SDST scores, while that of WORD vs ALL model negatively correlated with pre-scan SDST score (r = -0.558). The accuracy of rest vs MOTION during feedback scan 3 also correlated with pre-scan SDST score (r = 0.526), while the task predictive values during feedback scan 1 positively correlated with post-scan SDST score (r = 0.545) and the difference between pre- and post-scan SDST scores (r = 0.531). The task predictive values of MOTION vs ALL during feedback scan 1 and scan 3 also correlated with post-scan SDST scores with r = 0.568 and r = 0.510, respectively.

The difference between task predictive values of rest vs WORD classification model during feedback scans 3 and 1 were negatively correlated with pre-scan SDST score (r = -0.651), post-scan SDST score (r = -0.5901), and the questionnaire item related to the participant's performance during WORD task (r = -0.676). Finally, the distance measure of rest vs COUNT classification model during feedback scan 2 negatively correlated with word generation test score before the scan (r = -0.562) and the difference before and after the scan (r = 0.622). These strong correlations with behavioral test scores imply that the observed differences in accuracies and task predictive values were reflective of each individual's performance and not on the classification of the trained SVMs.

5．主な発表論文等

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６．研究組織

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